No Image

WO9919300A1: PROSTAGLANDIN AGONISTS AND THEIR USE TO TREAT BONE DISORDERS

No Image | View Cart

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LEFKER, Bruce, Allen , 21 Eagle Ridge Drive, Gales Ferry, CT 06355, United States of America
ROSATI, Robert, Louis , 71 Deans Mill Road, Stonington, CT 06378, United States of America

Applicant(s): **PFIZER INC.**, 235 East 42nd Street, New York, NY 10017, United States of America

Issued/Filed Dates: **April 22, 1999** / Oct. 5, 1998

Application Number: **WO1998IB0001540**

IPC Class: C07D 213/71; C07C 311/13; C07D 401/12; C07D 405/12; C07D 409/12; C07D 417/12; C07D 233/84; C07D 403/12; A61K 031/18; A61K 031/40; A61K 031/415; A61K 031/435; A61K 031/425; A61K 031/505;

Designated Countries: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, **European patent:** AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, **OAPI patent:** BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG, **ARIPO patent:** GH, GM, KE, LS, MW, SD, SZ, UG, ZW, **Eurasian patent:** AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

Abstract: This invention relates to prostaglandin agonists, methods of using such prostaglandin agonists, pharmaceutical compositions containing such prostaglandin agonists and kits containing such prostaglandin agonists. The prostaglandin agonists are useful for the treatment of bone disorders including osteoporosis.
[Show "fr" Abstract]

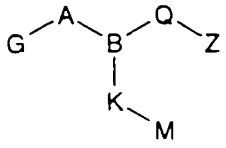
Attorney, Agent, or Firm: **SPIEGEL, Allen, J.;**

Foreign References: **none**

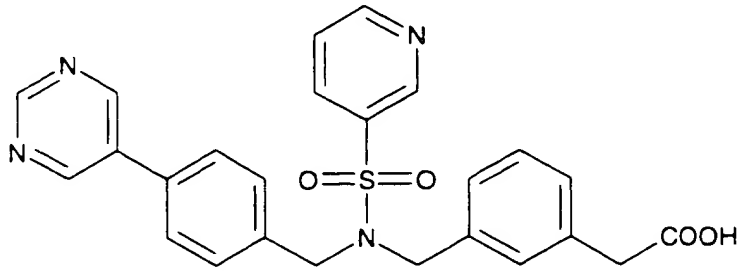
(No patents reference this one)

New prostaglandin agonists - useful for the treatment of bone diseases (e.g. osteoporosis), kidney degeneration and glaucoma.

Drug Activity: Osteopathic; Antiinflammatory; Nephrotropic; Ophthalmological; Hypotensive
Mechanism f Action: Prostaglandin-Agonist
Compound Name: None Given



(I)



(Ia)

Use: For the treatment of osteoporosis (e.g. glucocorticoid-induced osteoporosis), osteotomy, childhood idiopathic bone loss or bone loss associated with periodontitis; for augmenting and maintaining bone mass (e.g. following facial reconstruction or treating bone fracture); for treating kidney degeneration, glaucoma, ocular hypertension (claimed) and as prostaglandin agonists.

Dosage: 0.001-100 (0.01-10) mg/kg/day. Administration may be systemic or local, such as oral, parenteral and intraduodenal.

Advantage: None given.

Biological Data: No data given.

Chemistry: Compounds of formula (I) and their prodrugs and salts are new.

A = SO2 or CO; G = a defined aryl or bi-aryl containing group, arylamino, or R1R2-amino.

R1,R2 = H or alkyl, or together NR1R2 is a 5/6-membered heterocycle; B = N, or CH; Q = a defined divalent linking group such as alkylene optionally substituted and optionally interrupted by an aromatic ring.

Z = carboxyl, alkoxycarbonyl, tetrazolyl, 1,2,4-oxadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, alkylsulfonylcarbamoyl, or phenylsulfonylcarbamoyl; K = a bond, or alkylene optionally substituted and optionally interrupted by O or S; M = defined aryl, or defined biaryl (in which the aryl groups are linked via a heteroatom, a divalent linking group (e.g. alkylene) or directly by a bond); Provisos are given.

Several compounds are specifically claimed e.g. (3-(((pyridine-3-sulfonyl)-(4-pyrimidin-5-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid (Ia) (example Ia).

249 pages Drawings 0/0

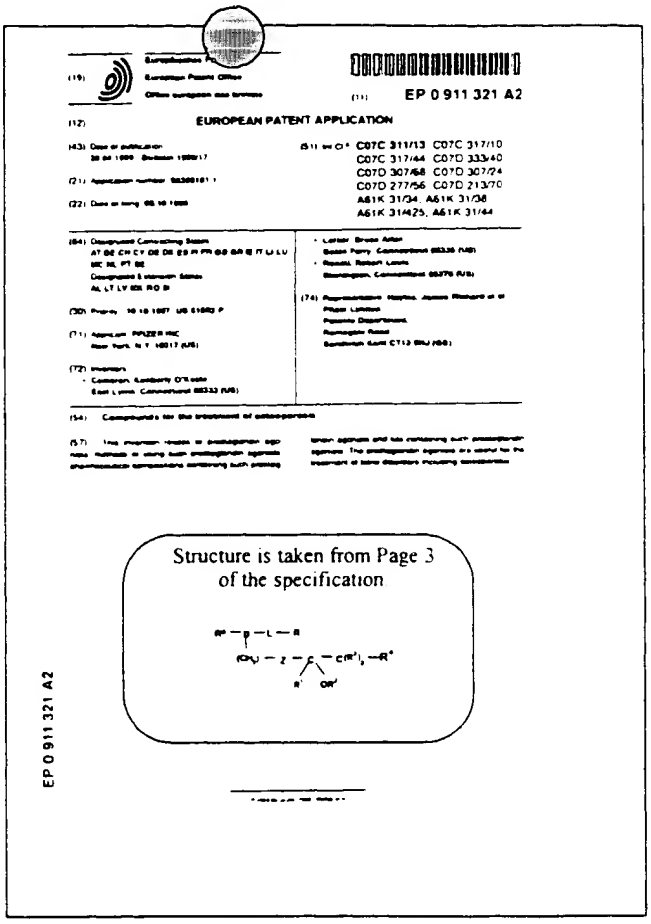
Authors: Cameron K O; Lefker B A; Rosati R L
Location: New York, N.Y., USA

Publication Date: 22 April 1999
Document Number: WO9919300-A1
Language: English
Filed: 05 October 1998 as IB1540
Priority: 10 October 1997 US-061727
Designated States: Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE (ARIPO) (Eurasian) (OAPI) National: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

EP911321

Pfizer

Prostaglandin agonists used in the treatment of osteoporosis. *See* WO9827976 and WO9828264.



EP 0 911 321 A2

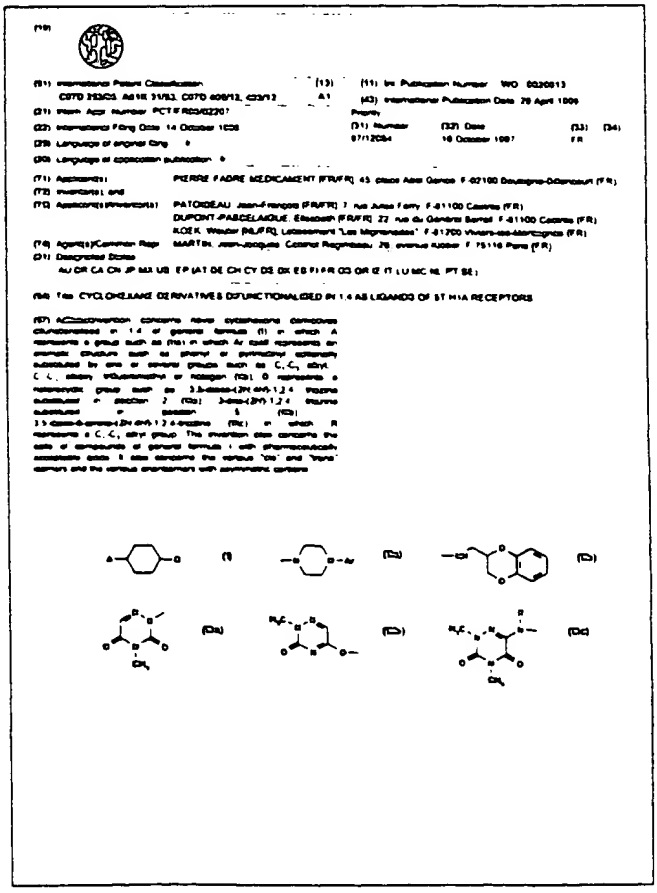
EUROPEAN PATENT APPLICATION

Structure is taken from Page 3 of the specification

WO9920613;
WO9920622

Pierre Fabre

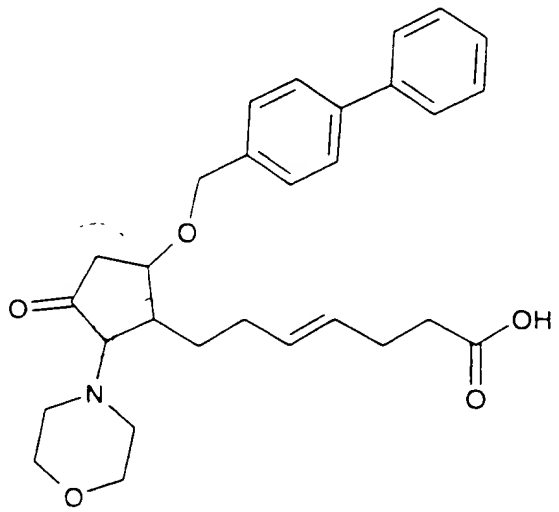
1-4 Difunctionalised cyclohexane and 3-oxo-2(H)-1,2,4-triazine derivatives as 5-HT_{1A} receptor ligands. Related to compounds claimed by Patoiseau and Dupont-Passelaigue in WO9501965 and WO9616949.



Use of EP4 receptor antagonists as bone resorption inhibitors - for the treatment of osteoarthritis, rheumatoid arthritis, osteoporosis, inflammatory bone diseases and hypocalcemia.

Drug Activity: Osteopathic; Antiarthritic; Antirheumatic; Antiinflammatory; Cardiovascular-Gen.
Mechanism of Action: Prostaglandin-Antagonist-EP4; Prostaglandin-Antagonist-E2
Compound Name: None Given

(I)



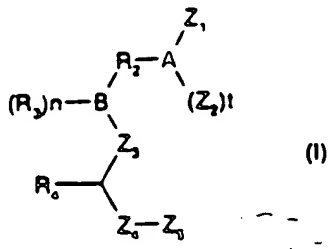
Use: As EP4 antagonists for the treatment of conditions with accelerated bone resorption (claimed) e.g. osteoarthritis, rheumatoid arthritis, osteoporosis, inflammatory bone diseases and hypocalcemia.
Dosage: 0.1-200 (0.1-10) mg/kg/day. Administration may be oral, parenteral, rectal or by inhalation.
Advantage: The compounds prevent accelerated bone resorption by inhibiting PGE_2-stimulated osteoclast-like cell formation in bone marrow.
Biological Data: None given.
Chemistry: The use of an EP4 antagonist in the treatment of conditions with accelerated bone resorption is claimed.
Preferably the EP4 antagonist is [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid (I) or its [1R[1α(Z),2β,5α]]-(-)-isomer or their salts and solvates.

7 pages Drawings 0/0

Authors: Foord S M; Sheldrick R L G; Lumley P
Location: Greenford, U.K.
Publication Date: 21 April 1999
Document Number: GB2330307-A
Language: English
Filed: 07 February 1998 as 002599
Priority: 07 February 1998 GB-002599

New sulfonamide and carboxamide derivatives bind to prostaglandin E2 receptors - useful for e.g. promoting and inhibiting digestive tract m tility, causing analgesia and as hypotensives.

Drug Activity: Inotropic-Pos.; Inotropic-Neg.; Gynecological; Gastrointestinal-Gen.; Analgesic; Sedative; Vasotropic; Hypotensive; Diuretic; Antidiarrheic; Antidiabetic; Antiulcer; Antiinflammatory; Tocolytic; Laxative; Tranquilizer
Mechanism of Action: Prostaglandin-Agonist-E2; Prostaglandin-Antagonist-E2
Compound Name: None Given



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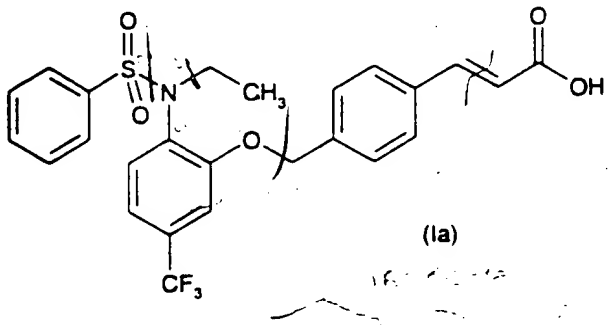


(Ia)

Use: As antagonists and agonists of prostaglandin E2 (PGE2) receptors for promoting or inhibiting uterine muscle contraction or digestive tract movement, as analgesics or hypnotics, for enlarging vascular capacity, for suppressing gastric acid secretion, and as hypotensives or diuretics, for treating diarrhea, diabetes, gastric ulcers, pruritus, to aid sleep and as antiabortifacient, laxatives and tranquilizers.
Dosage: 1 µg-100 mg/day orally or 0.1 µg-10 mg/day parenterally.
Advantage: None given.
Biological Data: In a PGE2 receptor binding assay (Ia) had a Ki of 0.0002 µM.
Chemistry: Sulfonamide and carboxamide derivatives of formula (I) and their salts are new.
ring A, ring B = 5-15C carbocyclyl or 5-7 membered heterocyclyl containing 1 or 2 O, N or S; Z1 = COR1, 1-4C alkylene-COR1, CH=CHCOR1, C≡CCOR1, O-1-3C alkylene-COR1, or 1-5C alkylene-OH; R1 = OH 1-4C alkoxy or optionally substituted NH2; Z2 = H, 1-4C alkyl, 1-4C alkoxy, NO2, halo, CF3, CF3O, OH or COR1; Z3 = bond or 1-4C alkylene; Z4 = SO2 or CO; Z5 = 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, optionally substituted cycloalkyl, phenyl or heterocyclyl or substituted alkyl, alkenyl or alkynyl; R2 = O, S, CO, or optionally substituted imino, CONH, NHCO or alkylene; R3 = H, 1-6C alkyl, 1-6C alkoxy, 1-6C alkylthio, NO2, halo, CF3, CF3O, OH or CH2OH; R4 = H, 2-8C alkenyl, 2-8C alkynyl or optionally substituted alkyl; a, t = 1-4; provided that when A = a benzene ring and (Z2)t = COR1 then Z1 is bonded to the 3 or 4 position of A.
(I) is e.g. 4-[2-(N-ethylphenylsulphonylamino)-5-trifluoromethylphenoxymethyl] cinnamic acid (Ia).

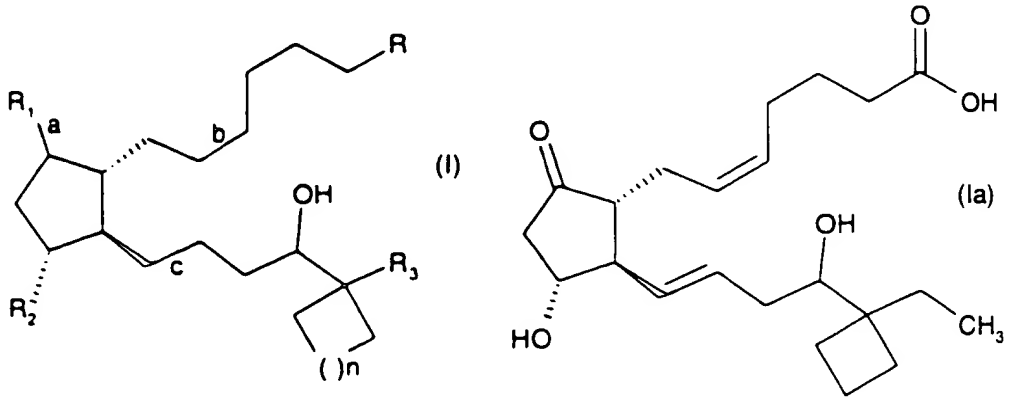
305 pages Drawings 0/0

Authors: Chuchida S; Nagao Y
Location: Osaka, Japan
Publication Data: 25 June 1998
Document Number: WO9827053-A1
Language: Japanese
Filed: 12 December 1997 as J04593
Priority: 21 October 1997 JP-305055
Designated States: Regional: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE Nati nal: AU CA CN HU JP KR MX NO US
WD-98-008828

TX 1-20-D

New ω-cycl alkylprostaglandin E2 derivatives are EP2 receptor modulators - useful f r the treatment of e.g. immunological diseases, asthma and abnormal bone formation.

Drug Activity: Immunomodulator; Antiasthmatic; Osteopathic; Neuroprotective; Hepatotropic; Antiinfertility; Tocolytic; Ophthalmological
Mechanism of Action: Prostaglandin-Antagonist-EP2; Prostaglandin-Agonist-EP2
Compound Name: None Given



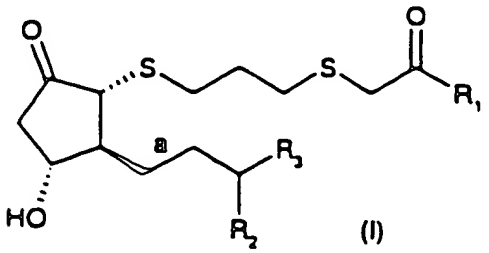
Use: As EP2 receptor modulators and for the treatment and prevention of immunological diseases, asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retina neuropathy of glaucoma (claimed).
Dosage: 1 ug-100 mg orally; 0.1 ug-10 mg parenterally. Administration is also rectal.
Advantage: Improved specificity and reduced side effects.
Biological Data: Compounds of the invention were assayed for activity against prostanoide receptor subtypes. Compound (Ia) showed K_i values of > 10, 0.030, > 10 and > 10 μM for receptors EP1, EP2, EP3α and EP4 respectively.
Chemistry: ω-Cycloalkyl-prostaglandin E2 derivatives of formula (I) and their salts and cyclodextrin clathrates are new.
R = COOH or CH2OH; R1 = oxo, CH2 or halo; R3 = alkyl, alkenyl, alkynyl (all optionally substituted) or H; n = 0-4; a = optional double bond; b = optional double or triple bond; c = optional single, double or triple bond; Provisos are given.
Several compounds are specifically claimed e.g. (5Z,11α13E)-11,16-dihydroxy-9-oxo-17,17-propano-20-norprosta-5,13-dienoic acid (Ia) (example 4(10)).

121 pages Drawings 0/0

Authors: Tani K; Ohuchida S
Location: Osaka, Japan
Publication Date: 26 August 1998
Document Number: EP-860430-A2
Language: English
Filed: 03 February 1998 as 300769
Priority: 06 November 1997 JP-319169
Designated States: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

New 3,7-diathiaprostanoic acid derivatives - useful for the treatment and prevention of e.g. immunological disease, asthma, abnormal bone formation and neuronal cell death.

Drug Activity: Immunosuppressive; Immunostimulant; Antiasthmatic; Osteopathic; Neuroprotective; Hepatotropic; Nephrotropic; Antiinflammatory; Hypotensive; Cardiant; Vasotropic
Mechanism of Action: Prostaglandin-Agonist-E2; Prostaglandin-Agonist-EP4
Compound Name: None Given



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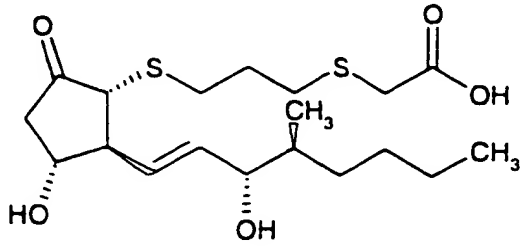


(Ia)

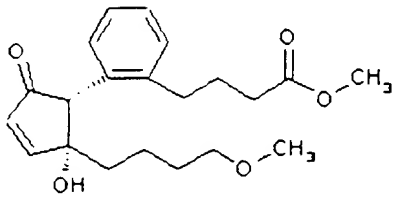
Use: For the treatment and prevention of immunological diseases e.g. autoimmune diseases, immunological deficiency diseases and organ transplantation, asthma, abnormal bone formation, neuronal cell death, liver damage, nephritis, hypertension and myocardial ischemia (claimed).
Dosage: 1 ug-100 mg orally up to several times per day; 0.1 µg-10 mg parenterally up to several times per day. Administration may also be topical, rectal or vaginal.
Advantage: None given.
Biological Data: Membrane fraction was prepared using the prostanoid receptor subtypes (mouse EP3α, EP4) expressing CHO cells. A standard assay mixture containing membrane fraction (0.5 mg/ml), 2.5 nM of ^{3}H-PGE_2 and various concentrations of the test compounds was incubated for 1 hour at room temperature. The reaction was terminated by the addition of ice-cold buffer. Kd and Bmax values were determined and non-specific binding was calculated as the bound in the presence of an excess of unlabeled PGE_2. The dissociation constant (K_i) was then determined, and (Ia) produced a K_i of 0.0002 µM for EP4 receptor subtypes.
Chemistry: 3,7-Dithiaprostanoic acid derivatives of formula (I) and their salts and cyclodextrin clathrates are new.
R1 = OH, 1-4C alkoxy or NR6R7; R6, R7 = independently H or 1-4C alkyl; R2 = H or OH; R3 = optionally substituted 1-8C alkyl, optionally substituted 2-8C alkenyl, optionally substituted 2-8C alkynyl, Ph or 3-7C cycloalkyl; a = double or single bond; the derivative may include the 8-epi equilibrium compound; provisos are given.
Several compounds are specifically claimed e.g. 11α,15α-dihydroxy-9-oxo-16β-methyl-3,7-dithiaprost-13E-enoic acid (Ia) (Example 2(o)).

39 pages Drawings 0/0

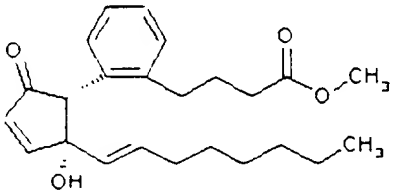
Authors: Maruyama T; Ohuchida S
Location: Osaka, Japan
Publication Date: 29 July 1998
Document Number: EP-855389-A2
Language: English
Filed: 26 January 1998 as 300513
Priority: 27 January 1997 JP-027198
Designated States: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
WD-98-009700

[April 16, 1999] New series of osteogenesis-promoting agents developed at Taisho

Taisho scientists have prepared and evaluated two series of **phenyl-substituted hydroxycyclopentenone analogues with osteogenesis-promoting effects**. Compounds of the invention were found to significantly increase Ca2+ and alkaline phosphatase (ALP) in human long bone osteoblast cultures at a concentration of 5 mcM (JP 99043460 and JP 99043459).



JP 99043460

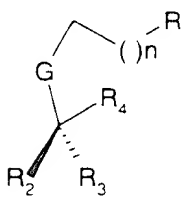


JP 99043459

‹ BACK SEARCH FORM

Use of tetrahydrofuran prostaglandin analogs as prostaglandin DP/FP receptor agonists - for the treatment of glaucoma and ocular hypertension.

Drug Activity: Ophthalmological; Hypotensive
Mechanism of Action: Prostaglandin-Agonist
Compound Name: None Given



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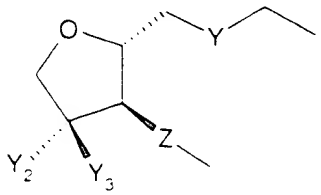
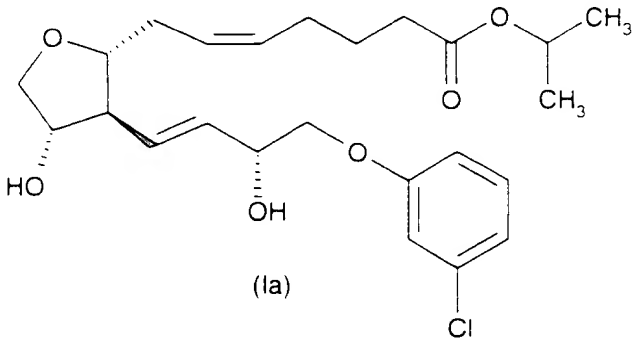


(i)



(Ia)

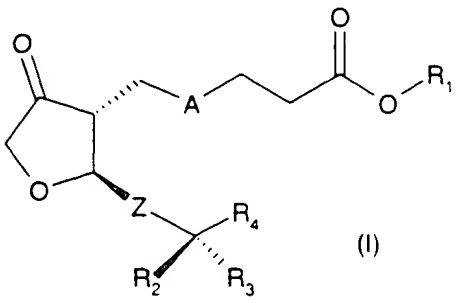
Use: For treating glaucoma and ocular hypertension (claimed). As agonists at the prostaglandin DP and FP receptors.
Dosage: 0.00003-0.5 (0.001-0.01) wt% solution for topical administration to the eye.
Advantage: Improved therapeutic profile compared to natural prostaglandins.
Biological Data: No data given.
Chemistry: The use of prostaglandin analogs of formula (I) for treating glaucoma or ocular hypertension is claimed.
R = an ester, CO2R1, CONR7R8, CH2OR9 or CH2NR10R11; R1 = H, or a cationic salt or ammonium moiety; R7,R8 = independently H or alkyl; R9 = H, acyl, or alkyl; R10,R11 = independently H,acyl or alkyl (providing only one is acyl); n = 0 or 2; G = a group of formula (i) or two other defined tetrahydrofuran containing moieties; Y = CH2CH=CH (cis), CH=CHCH2 (cis) or CH2CH2CH2; Z = CC, CH=CH (trans) or CH2CH2; one of Y2,Y3 = H, and the other = F or OH (which may be modified); R4 = cyclohexyl, 5-7C alkyl or R5; R5 = (CH2)mXphenyl or (CH2)pZ2; X = O or CH2; m = 1-6; phenyl is optionally substituted with halo, CH3, CF3, CN, OCH3 or acetyl; p = 0-6; Z2 = a defined optionally substituted bicyclic carbocycle or O-containing heterocycle; Several provisos are given.
(I) is e.g. isopropyl [2R(5Z),3S(1E,3R),4S]-7-[tetrahydro-3-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-2-furanyl]-5-heptenoate (Ia) (compound VI).

24 pages Drawings 0/0

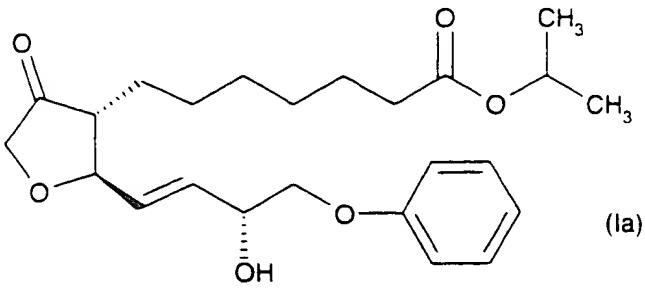
Authors: Selliah R D
Location: Fort Worth, Tex., USA
Publication Date: 23 December 1998
Document Number: WO9857942-A1
Language: English
Filed: 03 June 1998 as U11339
Priority: 18 June 1997 US-878030
Designated States: Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE National: AU BR CA JP MX US

Use of tetrahydrofuran prostaglandin analogs as prostaglandin EP receptor agonists - for the treatment of glaucoma and ocular hypertension.

Drug Activity: Ophthalmological; Hypotensive
Mechanism of Action: Prostaglandin-Agonist
Compound Name: None Given



(I)



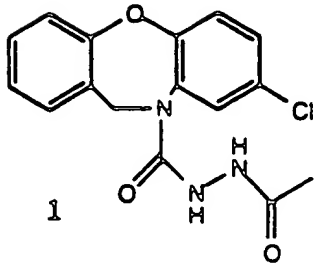
(Ia)

Use: For treating glaucoma or ocular hypertension (claimed). As agonists at the prostaglandin EP receptor.
Dosage: 0.00003-0.5 (0.001-0.01) wt% solution for topical administration to the eye.
Advantage: Improved therapeutic profile compared to natural prostaglandins.
Biological Data: No suitable data given.
Chemistry: The use of prostaglandin analogs of formula (I) for treating glaucoma or ocular hypertension is claimed.
R1 = H, 1-5C alkyl, 3-6C cycloalkyl or a cationic salt moiety; A = CH2CH=CH (cis), CH=CHCH2 (cis) or CH2CH2CH2; Z = CC, CH=CH (trans) or CH2CH2; One of R2,R3 = H, and the other = F or OH (which may be modified), or R2 and R3 together = OCH2CH2O, or carbonyl; R4 = (CH2)mXphenyl or (CH2)pZ2. X = O or CH2; m = 1-6; phenyl is optionally substituted with halo, CH3, CF3, CN, OCH3 or acetyl. p = 0-6; Z2 = a defined optionally substituted bicyclic carbocycle or O-containing heterocycle.
The use of isopropyl [2R(1E,3R,3R]-7-[tetrahydro-2-(4-phenoxy-3-hydroxy-1-butenyl)-4-oxo-3-furanyl]heptanoate (Ia) (compound III) is specifically claimed.

23 pages Drawings 0/0

Auth rs: Selliah R D
Publication Date: 23 December 1998
Language: English
Pri rity: 18 June 1997 US-878031
Location: Fort Worth, Tex., USA
Document Number: WO9857930-A1
Filed: 03 June 1998 as U11340
Designated States: Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE National: AU BR CA JP MX US
WD-99-000791

EP antagonists



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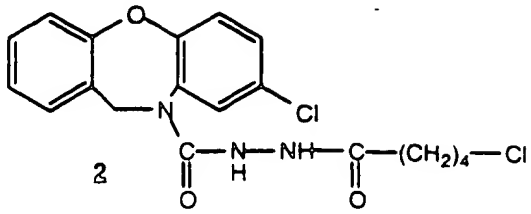
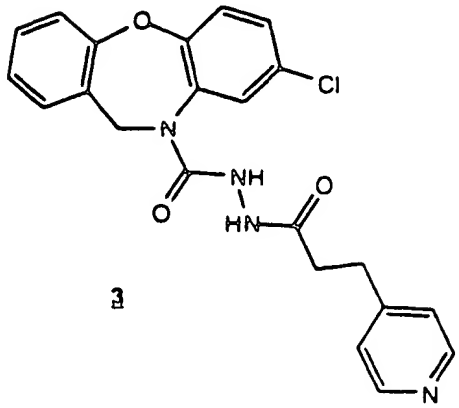


2



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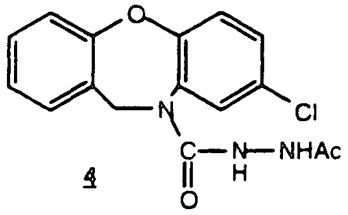

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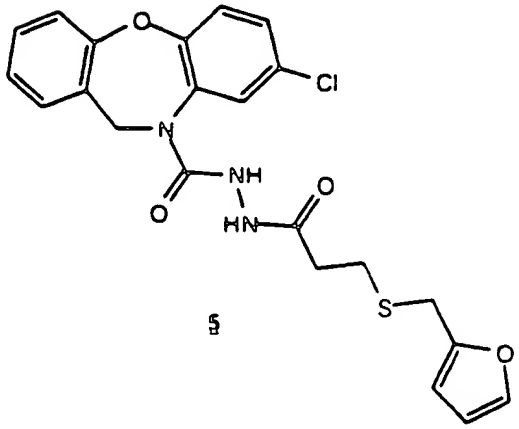

5

Recently, additional evidence for the involvement of PGE_2 and hence EP receptor subtypes in inflammation and pain has been reported. Specific monoclonal antibodies to PGE_2 (termed 2B5), that neutralize the activity of PGE_2, were efficacious in a phenylbenzoquinone-induced model of nociception (20). Furthermore, these antibodies could reverse established hyperalgesia in a carrageenan-induced hyperalgesia model (21). The 2B5 antibodies were also able to substantially reverse edema formation in a rat adjuvant-induced arthritis model (21). Remarkably, the efficacy of 2B5 in these inflammatory models was indistinguishable from that of indomethacin, a potent NSAID. In the most recent study, 2B5 was shown to be as efficacious as the COX-2 selective inhibitor, SC-58635, in a carrageenan-induced hyperalgesia model in rat (22). It is clear from these as well as previous studies that blockade of EP subtype receptor(s) could conceivably be as efficacious as NSAIDs in the treatment of inflammatory diseases without any of the undesirable side-effects associated with them.

Gastric Antisecretory and Cytoprotective Agents - PGs, especially PGE_2, are known to have mucosal protective effects and act through a number of different mechanisms